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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/351,778	07/12/99	WOLD	W 16153-7775

EXAMINER

HM12/0315

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ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/351,778	Wold et al.
Examiner	**Group Art Unit**
Peter Brunovskis	1632

☒ Responsive to communication(s) filed on *Oct 10, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-27* is/are pending in the applicat

Of the above, claim(s) *6-9, 16-19, 23, and 25-27* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 10-15, 20-22, and 24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

The Examiner for the instant application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed in accordance with the instructions at the end of this Action.

Election/Restriction

Applicant's election without traverse of Group I, claims 1-5, 10-15, 20-22, and 24 in Paper No. 9, filed 10/10/00 is acknowledged.

Claims 6-9, 16-19, 23, and 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 10-15, 20-22, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) is indefinite in its recitation of "recombinant vector" relative to "replication-competent" in view of claim 3 presuming to further limit the claimed subject matter by reciting "the recombinant vector...which comprises a recombinant virus". To the extent that claim is drawn to recombinant vectors that are not recombinant viruses, such as plasmid vectors, it is not clear what "replication-competent" means. Further the claim is indefinite in its recitation, "which overexpresses an adenovirus death protein" inasmuch as the term implies there to be *other* death proteins, in addition to *adp* (i.e. E3-11.6 kDa protein). Changing the phrase to phrase to --which overexpresses the adenovirus death protein (E3-11.6 kDa protein)-- would obviate the problem.

Claims 1 and 10 (and dependent claims) are indefinite in their recitation of the phrase, "which overexpresses an adenovirus death protein" since it is unclear what context "overexpresses" is directed or applied to (i.e. overexpresses relative to what?). For example, wild-type adenoviruses typically "overexpress" adp at very high levels at very late stages of infection; thus, a reasonably broad interpretation of the rejected claims would suggest that any adenovirus carrying adp operatively linked its native promoter inherently meets the limitation of the claims as written.

Claims 2 and 11 (and dependent claims) are indefinite in their recitation of the phrase, "comprises amino acids 1-26, 41-59, and 63-70" since it is unclear whether these limitations are only directed to SEQ ID NO:5, or whether they are also directed to SEQ ID NOs:6, 7, and 8. In

addition, it is unclear what SEQ ID NOs the phrase "or conservatively substituted variant thereof" is directed to, nor is it clear how the phrase is defined or what its metes and bounds are.

Claims 5 and 15 are indefinite in their recitation, "recombinant vector [or recombinant adenovirus] of claim 4 which comprises SEQ ID NO:3 or SEQ ID NO:4" since it is unclear what structural relationship exists between the sequences set forth in SEQ ID NOs:3 and 4 and "[t]he recombinant vector [or adenovirus] of claim 4". For example, it is unclear whether the sequences are directed to e.g. nucleic acids of recombinant virus vector genomes or whether they broadly embrace e.g. plasmids DNAs comprising said sequences conjugated to an inactivated adenovirus particle.

Claim 10 (and dependent claims) is indefinite in its recitation of the term "contacting" or the phrase "which overexpresses an adenovirus death protein" relate back to the preamble reciting "a method for promoting death of a neoplastic cell" or to the vector which is replication competent. Specifically, it is unclear what is meant by "contacted" in the context of the cell--i.e. whether it is sufficient to "contact" the cell with the vector to promote death or whether the cell requires the vector to "transfect" or of "infect" the cell. Further, it is not clear whether the method requires a replication competent vector to overexpress an adenovirus death protein or whether the method requires that neoplastic cells expressing an adenovirus death protein be contacted with a replication competent vector.

Claim 13 (and dependent claims) is indefinite in its recitation of the phrase, "wherein the neoplastic cell comprises a tumor" since a cell is not capable of comprising a tumor, which

consists of a *plurality* of cells. Changing the the term "comprises" to --is contained in-- would obviate the problem.

Claim 13 (and dependent claims) is indefinite because it is unclear how the contacting step of claim 13 relates to the contacting step of base claim 10, inasmuch as claim 10 recites "contacting [a] neoplastic cell" whereas the instant claim redefines "contacting" as directed to "administ[ration] to the tumor". Changing the phrase to --administering the recombinant adenovirus to neoplastic cells of a tumor-- would obviate the problem.

Claim 14 (and dependent claim 15) is indefinite in its recitation of the phrase, "passively immunizing the patient against the recombinant adenovirus" since it is unclear how this limitation relates back to the preamble reciting "[a] method for promoting cell death".

Claims 13, 14, 15, and 24 (and dependent claims) recite the limitation "the recombinant adenovirus". There is insufficient antecedent basis for this limitation in the claims, since the claims to which this limitation depend (e.g. claims 12, 13 etc.) embrace recombinant non-adenoviral vectors in addition to recombinant adenovirus vectors explicitly recited in claim 12, for example.

Claim 21 is indefinite in its recitation "comprising more than one recombinant adenovirus" since any treatment would inherently comprise administration of more than one recombinant adenovirus. Specifically, it is not clear whether the claim is drawn to more than one different and distinct types of recombinant adenoviruses, for example.

Claim 24 is indefinite in its recitation of the phrase "complements spread of the replication-defective adenovirus in the tumor" since it is unclear what structural relationship exists

between the replication competent and the replication-defective adenoviruses or what definition or the metes and bounds apply to the term "complements" in the context of the claim.

Claims 1-5, 10-15, 20-22, and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The claimed invention is drawn to methods and compositions comprising a replication-competent vector overexpressing an adenovirus death protein and its use in methods for promoting neoplastic cell death. The specification does not present any specific, substantial, or

well-established utility for using the recombinant vectors other than in vivo therapeutic methods for treating cancer. Therefore, the compositions and methods are evaluated as to whether the specification provides an enabling disclosure for in vivo cancer therapy. With regard to the non-enabled compositions and methods as they are drawn to therapeutic gene delivery, it is noted that at the time filing, successful use of gene therapy was not routinely obtainable by those skilled in the art. W. French Anderson, one skilled in the art, recently concluded: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make" (p. 30, next to last paragraph). Concurring with Anderson, Verma and Somia state that "[t]he Achilles heel of gene therapy is gene delivery...and [t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (Nature, vol. 389, 1997, p. 239, col. 3, 2nd paragraph)...[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239, col. 1, 2nd paragraph).

Despite being considered by some as the "gold-standard" for gene transfer, adenoviral vectors were recognized at the time of filing as yet to have been developed to overcome the problems described by Anderson and Verma. Curiel reviewed the state of the adenoviral vector art as it relates to gene therapy as follows:

> "To date, several groups have sought to exploit the fundamental advantages of adenovirus by using it in specific contexts where the recognized limitations were judged to be less important. For example, it was thought that the issue of the widespread tropism of the virus could be circumvented by administering the vector by direct injection, particularly in the context of tumors. However, in phase I human trials, dissemination beyond the injected site was found. Application to "compartmentalized" disease has also met with problems. For example, poor gene transfer efficiency has been noted following administration into the pleural space for therapy of mesothelioma, and in the peritoneum, effective use of antitumor gene therapy has been limited by concurrent gene transfer of the liver with subsequent toxicity. Further limitations have arisen in the application to pulmonary disease. Here, prior clinical experience had indicated that the virus had a natural tropism for the respiratory tract; therefore, direct administration of vector to the airways for cystic fibrosis therapy seemed a rational approach. In reality, the achieved levels of gene transfer were lower than expected, because differentiated airway epithelial cells lack sufficient adenoviral receptors and the integrins required for viral internalization. Therefore, even in these apparently favorable anatomic locations there is a strong case for developing a vector with cell-specific targeting properties" (p. 159, Ann. NY Acad. Sci., 886:158-171, 1999).

Furthermore, in reviewing the use of vectors for gene therapy of cancer at the time of filing, Gomez-Navarro et al. taught that "transduction efficiencies of presently available vectors have been shown to be inadequate. Even in the context of closed compartment delivery, it has not been possible to modify a sufficient number of tumour cells to achieve a clinically relevant tumoral response (p. 873, right col., Eur. J. Cancer, 35(6):867-885, 6/99).

On the other hand, Gomez-Navarro also taught that:

> "[o]ne method to circumvent suboptimal tumour transduction of therapeutic genes in vivo would be the use of conditionally replicative viral vectors: a replication-competent virus would be employed to replicate selectively within infected tumour cells, leaving normal tissues unaffected. Production of progeny virions from the infected tumour cells would then allow infection of neighboring tumour cells. Thus, the intratumoral viral inoculum would increase, improving the tumour transduction efficiency. In addition, the use of viruses that display a lytic life cycle would allow virus-mediated oncolysis. This effect would occur irrespective of the delivered transgene" (p. 875, left col.).

The teachings of Gomez-Navarro are basically in accordance with Applicants general approach and objectives. However, a number of factors or considerations underscore the unpredictability associated with this approach.

In fact, the physiological art is recognized in general as being unpredictable (MPEP 2164.03). As set forth *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

However, in view of the failures associated with attempts to treat diseases by gene therapy as taught by Anderson and Verma, the problems and challenges concerning use of vectors for cancer gene therapy as taught by Curiel and Navarro-Gomez, and the paucity of clinical success in cancer gene therapy, in the absence of relevant working examples, any attempts to treat cancer by gene therapy should be considered highly unpredictable. This unpredictability is echoed in recent

discussion concerning attempts to engineer conditionally replicative adenoviruses selectively targeting p53 mutant tumour cells in accordance with the teachings of Gomez-Navarro above. In spite of "encouraging preliminary reports", Gomez-Navarro reported that "extensive studies in a variety of cell lines and animal tumour models have to date failed to confirm the selective properties of the virus to replicate only in p53 mutant tumour cells" (p. 875, right col.). Gomez-Navarro teaches that selective gene delivery is necessary because the number of vector particles available for delivery to the cancer cells would be decreased by sequestration by normal, nontarget cells" (p. 877, left col.).

However, Gomez-Navarro notes that:

> "attempts in the prior art to restrict expression of the therapeutic gene to the target cancer cells merely by confining vector administration have proved inadequate...[and that] locally administered adenoviral vectors carrying the HSV-tk gene have been shown to disseminate, probably as a result of leakage into the blood stream, resulting in a high level of liver-associated toxicity...[i]n addition, in situ injection of adenoviral vectors has been associated with a low level of efficiency of gene transfer to the disease cells in human clinical trials. This phenomenon has been correlated with a paucity of primary receptors on the cancer cells. Hence, it is apparent that there is a need to develop a vector which will achieve a high efficiency of gene transfer selectively to target tumour cells following compartmentalised administration in order to increase the therapeutic index and realise the full potential of gene therapy as a safe approach to the treatment of cancer" (p. 877, right col.).

Although Applicants disclosure envisions the use of cell specific- or tumor-specific promoters to provide conditional replication in tumor cells infected by the recombinant adenoviruses of the instant invention, their disclosure fails to address selective delivery at the level of the tumor cell. The claimed adenoviral vectors are no different with respect to ubiquitously

targeting and infecting a broad range of non-tumor cells carrying the coxsackie-adenovirus receptor (CAR). However, even if vectors could be designed, or modes of administration could be developed to avoid infection of non-tumor cells, in the absence of specific guidance or relevant working examples, treatment of tumors is highly unpredictable given the "paucity of primary receptors on the cancer cells" as taught by Gomez-Navarro, as indicated by the analyses of Li et al. (Cancer Res., 59:325-330, 1/15/99) who recently reported variability in the sensitivity to viral infection in several human bladder cancer lines due to differences in viral receptor (i.e. CAR) expression levels. These differences were interpreted by Li et al. to suggest that variability in sensitivity "may have a significant impact on the outcome of adenovirus-based gene therapy" (see abstract and p. 329, left col.). Analogous results were obtained upon analysis of adenoviral infectivity of melanoma- (Hemmi et al., 9:2363-2373, 11/1/98) and head and neck squamous cell carcinoma (HNSCC) cell lines (Li et al., Clin. Cancer Res., 5:4175-4181, 12/99). The instant specification fails to provide sufficient guidance for one of ordinary skill to determine which tumor target cells carry the requisite level of adenoviral receptors so as to allow the possibility of producing a predictable therapeutic benefit in accordance with the claimed method.

Moreover, with respect to in vivo delivery to tumors, there is essentially no guidance concerning the specific routes of adenoviral vector administration for a given tumor, nor any specific guidance concerning delivery across the blood-organ or blood-brain barriers. At the time of filing Jain reviewed the multiple barriers limiting delivery of therapeutics to solid tumors and teaches that "tumors often develop in ways that hinder each of these [delivery] steps" (J. Contr.

Rel., 53:49-67, 4/1998; see e.g. abstract, p. 49). Moreover, Hobbs taught that different tumors exhibit varying degrees of vascular permeability reflected in pore cutoff sizes for therapeutic agent uptake depending on the tumor. In certain subcutaneous microenvironments, for example, these cutoff sizes were found to drop under certain conditions to less than 7 nm, significantly smaller than the size of adenoviral particles (Hobbs et al., Proc. Natl. Acad. Sci. USA, 95:4607-4612, 4/98; see e.g. p. 4607, right column). The specification does not address problems of delivery to solid tumors, nor does it provide a sufficient expectation of a therapeutic benefit using the claimed compositions commensurate with the claimed subject matter.

In view of the significant unpredictability, the multiple problems and challenges, the lack of correlation between in vitro and in vivo results, and the general lack of success in the cancer gene therapy art, to overcome the unpredictability and problems in the art and enable the instantly claimed methods commensurate with the broad scope of the claimed subject matter, the specification would need to supply direct, correlative guidance as to specific replication-competent adenovirus embodiments and the specific types of tumors that are treatable with said embodiments. This requires working examples obtained from appropriate and relevant animal model systems with specific details concerning the genetic construction of the adenovirus, the nature of any transgenes or promoters for replication and/or transgene expression, therapeutic expression levels (if applicable), routes of delivery, and dosage amounts/frequencies effective for alleviating symptoms of disease using the claimed replication-competent adenoviruses and/or replication-defective adenoviruses. However, the only animal models described in the instant

specification concern the use of KD1 or KD3 (i.e. Example 4) or combinations comprising KD1, KD3, GZ1, or GZ3 in conjunction with radiation (i.e. Example 8) to inhibit the growth of human tumors in nude mouse models. One of the problems with nude mouse models is that there is not a good correlation between results obtained using the same adenoviral cell killing system in immunodeficient animals as compared to results obtained in immunocompetent animals, as exemplified by results obtained in immunocompetent rats, where the response rates were significantly lower than in immunodeficient rats (Elshami et al., Hum. Gene Ther., 7:141-148, 1/20/96). Furthermore, with regard to would-be gene-therapy compositions comprising adenovirus vectors, recent clinical trials in humans have shown that the vectors are "not reliable in delivering genes where they are targeted", that they distribute differently in humans as compared to animals, "that they sometimes provoke or otherwise disrupt cytokine-determined inflammatory responses", and that "the doses at which there are toxic effects or potential therapeutic effects may be separated only narrowly...[wherein]...there may be threshholds where adverse effects abruptly appear - complicating how vectors might be used and perhaps undermining the reliability of results from tests in animals" (Fox, Nature Biotechnol., 18(2):143-144, 2/2000).

Further, in the context of immunocompetent animals, Applicants claimed invention comprising deletion of adenoviral E3 genes, can be considered an unpredictable "two-edged sword" against cancer treatment. This is due to the fact that Applicants recombinant vectors are deficient in immunoprotective adenoviral genes; by lacking these genes, one would predict a stronger immune response against the recombinant adenoviruses. However, a stronger immune

response would potentially limit cytolytic spread of the adenovirus replication in tumors. In the absence of results obtained in immunocompetent animals, there is no way of knowing a priori which process will be dominate, i.e. cytolytic spread of virus in tumors or cytotoxic T cell death effectively neutralizing the spread of the cytolytic infection to critical, uninfected tumor cell targets.

It should be noted for the record that Applicants claimed invention embraces a wide breadth of embodiments for use in the claimed methods that are not accompanied by sufficient guidance for one of skill in the art to use. For example, the specification only describes the use of adenovirus vectors for use with the claimed methods. However, the instant claims appear to broadly embrace nonviral replication-competent and/or non-adenoviral replication-competent viral vectors for use with the claimed methods (compare e.g. claims 1, 3, and 4) without sufficient and specific guidance concerning what these vectors are or how to design them in accordance with the intended purpose recited in the claimed methods.

Furthermore, the specification broadly embraces recombinant vectors comprising variants of the adenovirus death protein (ADP; see e.g. claims 2 and 11) without providing sufficient guidance on how to make and use variants that possess the appropriate properties shared by the wild type ADP in accordance with the intended methods and goals. Rudinger has stated that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by *painstaking experimental study*" (emphasis added; p. 6, 2nd to last sentence *In* J.A. Parsons, ed., "Peptide

hormones", University Park Press, 1976). The specification is not enabled for the breadth of subject matter directed to claims 2 and 11, since it fails to teach what conservatively substituted amino acids can be incorporated or added in addition to amino acids 1-26, 41-59, and 63-70 so as *maintain* the functional integrity to promote cell death in accordance with the methods and goals of the instant invention. For example, ADP variations increasing cell death potential could kill the cell before the virus has even had a chance to replicate (and spread). The specification fails to provide any guidance as to the specific nature of variant ADP embodiments that would work in the claimed methods.

Additionally, claim 14 recites a method comprising the step of "passively immunizing the patient against the recombinant adenovirus". However, the specification does not provide sufficient guidance concerning the purpose of this step, or the nature and timing of the specific compositions used in this step, beyond the mere germ of the idea presented on p. 20 lines, 17-22.

Moreover, claim 24 recites a method for promoting neoplastic cell death comprising the use of a replication competent vector *and* a replication-*defective* adenovirus. However, the specification fails to provide sufficient guidance or rationale for using these two qualitatively different types of vectors. For example, it not appear clear to one of skill in the art what benefit is achieved by mixing replication competent and replication-defective vectors. While the replication competent vector would be predicted to complement the replication and spread of the defective vector, it is not at all clear what benefit is gained by mixing the two, unless *both* were replication defective, but able to complement replication of each other so as to result in a limited infection

without the production (at least theoretically) of replication-competent vector. Although not explicitly mentioned, the only rationale for mixing these two types of vectors appears to be associated with a desire to achieve an optimal level or balance between replication and in vivo tumor cell spread. However, in the absence of specific guidance as to the proportion or nature of these two types of vectors, it would require undue experimentation to determine an effective combination or tumor to be treated with such in accordance with the claimed methods.

In the course of particular methods or compositions without sufficient guidance as to their purpose or specific nature (as in e.g. claims 2, 14, and 24) the claimed invention as such falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005).

In conclusion, given the unpredictable and undeveloped state of the art as described above, it would likely require considerable experimentation to appropriately develop the claimed invention commensurate with the scope of the claimed compositions and methods for promoting neoplastic cell death by gene therapy. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and relevant working examples in the specification, and the amount of experimentation necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Note: With respect to the claimed subject matter embracing in vivo therapeutic treatment, the following rejection applies to the extent that the claims read on methods involving e.g. use of vectors for *developing* therapeutic protocols to *test* various possible treatments for cancer gene therapy in experimental animals. The prior art rejections below are not to be construed as an indication that either the claimed- or anticipated methods are *enabled* for therapeutic use.

Claims 1-4 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Tollefson et al. (J. Virol., 70(4):2296-2306, 4/96).

Tollefson et al. discloses an Ad5 replication-competent adenovirus capable of overexpressing an adenovirus death protein and lacking expression of E3 proteins, including RIDα (also known as 10.4K), RIDβ (also known as 14.5K) and 14.7K (i.e. Ad5 dl309) and further disclose a method for promoting death of neoplastic cells in culture comprising infection of human A549 cells with said recombinant adenovirus (see e.g. Fig. 2 and "Materials and

Methods"). Inasmuch as the dl309 is from an Ad5 strain, the disclosure of Tollefson anticipates the broadly claimed "variant" subject matter recited in claims 2 and 11, particularly as directed to SEQ ID NO:7 (or variants thereof).

Claims 1-4 and 10-13 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Henderson et al. (U.S. 6,197,293, filed 3/02/98).

Henderson et al. discloses an E3-deleted replication-competent adenovirus, CN751, capable of overexpressing an adenovirus death protein, comprising the amino acid sequence of SEQ ID NO:6 (col. 69, SEQ ID NO:22) and further discloses methods for promoting death of neoplastic cells in cultured cells or tumors (see e.g. claims 3 and 20 and Example 6, col. 48-49).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 10-13, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (U.S. 6,197,293) as applied to claims 1-4 and 10-13 above in view of Freytag et al. (Hum. Gene Ther., 9:1323-1333, 6/10/98).

Henderson et al. was described above.

Freytag et al. discloses a novel three-pronged approach to kill cancer cells selectively comprising administration of a cytolytic replication-competent, E1B-attenuated adenovirus in conjunction with chemotherapy (i.e. suicide gene therapy employing virally encoded cytosine deaminase in conjunction with 5-FC) and radiation (see e.g. abstract and Fig. 8). Freytag teaches that the results demonstrate that "suicide gene therapy can enhance the therapeutic effects of viral therapy in a tumor cell-specific manner...[and that]...[t]he therapeutic effect of these combined modalities can be further enhanced by coupling them with radiotherapy" (p. 1328, right col.). Freytag further teaches that "because few human cancers are curable with a single modality, it has been our tenet that the promise of cancer gene therapy will be realized only when used in combination with other modalities, such as the ones described here...[offering]...a significant improvement over ONYX-015 because the three modalities may target different tumor cell types or subpopulations, which, in turn, should expand the spectrum of human tumors that it will be effective against (p. 1330, left col. and p. 1332, last paragraph).

At the time the invention was made it would have been obvious for one of ordinary skill in the art to combine the chemotherapy/radiation combination approach of Freytag when using the replication-competent adenovirus recombinant CN751 of Henderson, since Freytag teaches the enhanced cell killing properties when using a three-pronged approach involving additional modalities, combining a replication-competent adenovirus in conjunction with chemotherapy and radiation. Thus the invention was prima facie obvious at the time the invention was made.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
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Scott D. Priebe

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